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EXAMINER	
CANELLA, KAREN A	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,478	KISELEV ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *March 9, 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-13,26-33,35-45 and 75-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-13,26-33,35-45,75,76 and 80-89* is/are rejected.

7)☒ Claim(s) *77-79* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 4, 14-25, 34 and 46-74 have been canceled.. Claims 1, 3, 5, 13, 26, 31, 33, 35, 42, 75, 81, 83-85 and 88 have been amended. Claims 1-3, 5-13, 26-33, 35-45 and 75-89 are pending and under consideration..

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 1-3, 5-13 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record.

The term "low" in claim 1 is a relative term which renders the claim indefinite. The term "low" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Section 2173 of the M.P.E.P. states

Claims Must Particularly Point Out and Distinctly Claim the Invention

The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent..

In the instant case, the specification does not provide a limiting definition for a “low” immunogenicity which would provide a boundary between that which is “low” versus that which is not low, or “moderate”. Thus, a potential infringer would not be able to ascertain when a molecule was large enough not to be considered small, and therefore outside the scope of the claims..

Further, the immunogenic response to any given antigen is a function of the host as well as the antigen. It is unclear if an antigen of “low” immunogenicity is to be defined as having

"low" immunogenicity in humans or mammals, or if the antigen of "low" immunogenicity is to be defined as having "low" immunogenicity in the animal to be immunized.

Applicant argues that one of skill in the art would understand what constitutes "low" immunogenicity and that the specification provides numerous examples thereof. this has been considered but not found persuasive. While one of skill in the art would recognize many examples of "low" immunogenicity, the boundary between an antigen having what applicants consider a "low immunogenicity" and that what applicants considered as not having a "low immunogenicity" is unclear for the reasons stated above.

Claim 80 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear how claim 80 further limits the scope of claim 75 because the limitation of the carrier molecule being HSP70 is already a requirement of claim 75.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-13, 26-33, 35-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of claims 1, 14, 26, 46, 74, 75, 84 and 85, wherein the hybridoma is produced by a fusion with a non-human immortalized mammalian cell, does not reasonably provide enablement for the method of claims 1, 14, 26, 46, 74, 75, 84 and 85, wherein fusion to provide the hybridoma is with a human immortalized cell, or wherein the screening for specificity is based on a "protein A" assay. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988)..

Claims 11 and 43 require the use of an immortalized human cell as an acceptor for a B cell harvested from an immunized animal. The art teaches that chimeric hybridomas made by fusions of human B cells with mouse immortal cells are rare and that most such hybrids, with rare exceptions, tend to be highly unstable due to loss of human chromosomes (Kaplan, 'Monoclonal Human Antibodies', In: Monoclonal Antibodies in Clinical Medicine, McMichael and Favre, Ed.s, 1982, page18). It would be reasonable to assume that the converse hybridoma, that of a mouse B cell fused to an immortalized human myeloma cell would also be rare and subject to instability due to loss of the human chromosomes. Further, the art teaches that within rodent cells, some combinations of B cells and immortalized cell are less successful than others, for instance Milstein ('Monoclonal Antibodies from Hybrid Myelomas', In: Monoclonal Antibodies in Clinical Medicine, McMichael and Favre, Ed.s, 1982, page 9) and that the importance of the myeloma parental cell line should not be overlooked.. It is reasonable to conclude that not all combinations of activated B cell and immortalized cell will produce a stable chimeric hybridoma secreting antibody. The specification fails to address this unreliability in the art. Thus, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to carry out the claimed methods using an immortalized human cell as the fusion partner for an animal B cell.

Applicant argues that the references cites for lack of enablement are not representative of the knowledge at the time the application was filed. This is not persuasive. Applicant has not provided alternative references demonstrating that fusions between mouse B cells and human immortalized myeloma cells are not rare and subject to instability due to chromosomal loss. Applicant argues that the MPEP teaches that it is not necessary that one of skill in the art be able

to make and use a perfected commercially viable embodiment in order for the claims to meet the standard of 112, first paragraph. This has been considered but not found persuasive because that is not the standard being applied by the examiner. If fusions of mouse B cells and human immortalized myeloma cells are rare and subject to instability due to chromosomal loss, that is an indication of unreliability in the art, and one of skill in the art would be subject to undue experimentation in order to carry out the methods requiring such fusions.

Claims 13 and 45 require that the screening of the secreted antibody for specificity is carried out by a "protein A assay". Protein A is known to simply bind to the constant region of an IgG antibody, thus this type of binding would not serve to distinguish the abilities of the antigen-binding portions of the secreted antibody to bind to the specific antigen. One of skill in the art would be subject to undue experimentation is order to screen the secreted antibodies from the hybridomas using a protein A assay for IgG.

Applicant argues that a person of skill in the art would realize that a "protein A assay" does not simply refer to screening antibodies from the hybridomas for IgG and that " a patent need not teach, and preferably omits, what is well known in the art". This has been considered but not found persuasive. Claims 13 and 45 require that the screening for specificity be carried out by using the "protein A assay". As the protein A assay is not enabled to determine antigen-binding specificity for the reasons set forth above, the claim as drawn to this specific embodiment, is not enabled.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 83 is rejected under 35 U.S.C. 102(e) as being anticipated by Raven et al (WO 03/080665, filed October 2, 2003)..

Claim 83 is drawn to a kit comprising at least one reagent that specifically detects Prion protein and instructions for determining if the subject is at increased risk of developing spongiform encephalopathy, wherein the reagent is monoclonal antibodies produced by the method of claim 75 and instructions..

Section 2112.01 of the MPEP states:

Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. In re Ngai, F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004). See also In re Gulack, 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed. Cir. 1983).

Thus, in the instance case of claim 83, the specific disclosure of the instructions of section (b) in claim 83 does not provide patentable weight to distinguish the claimed kit from the kit of the prior art.

Raven et al disclose antibodies that bind to the peptide of SEQ ID NO:3 (claim 5) , wherein said SEQ ID NO:3 comprises the instant SEQ ID NO:6 peptide at residues 2-13:

Cys-Lys-Lys-Arg-Pro-Lys-Pro-Gly-Gly-Gly-Trp-Asn-Thr-Gly-Gly-Cys

Raven et al disclose that the invention includes monoclonal antibodies (page 8, lines 17-18). Thus the disclosure of Raven et al would inherently comprise monoclonal antibodies which bound to the instant peptide of SEQ ID NO:6. The instant claim 83 is a product by process claim which is dependent on the process of claim 75 to product the monoclonal antibodies of the kit. Section 2113 of the MPEP states:

PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)

.

In the instant case, the monoclonal antibodies of Raven et al that bind to SEQ ID NO:3 of the prior art application would have the same structural characteristics as the instant antibodies that bind to the instant SEQ ID NO:6 because said antibodies would recognize the same epitope on a prion protein. Therefore the disclosure of Raven et al anticipates the instant claim 83.

Claim 83 is rejected under 35 U.S.C. 102(b) as being anticipated by O'Rourke (WO01/05426).

O'Rourke discloses the monoclonal antibody of F99/97.6.1 which bound the epitope of Gln-Tyr-Gln-Arg-Glu-Ser (page 15, under "Epitope Mapping and Sequence Determination"-last paragraph), said epitope being within the instant SEQ ID NO:9

Ile-Thr-Gln-Tyr-Gln-Arg-Glu-Ser-Gln-Ala-Tyr-Tyr-Gln-Arg-Ala-Ser

Applying the same logic as in the rejection above over Raven et al, the monoclonal antibody of O'Rourke anticipates the instant claim 83.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 8-10 and 13 are rejected under 35 U.S.C. 103(a) as unpatentable over Cashman et al (U.S. 7,041,807) in view of Lussow et al (European Journal of Immunology, 1991, Vol. 21, pp. 2297-2302).

Cashman et al teach a method comprising immunizing mice with prion proteins conjugated to KLH, and the isolation of spleenocyte from the immunized mice to make hybridomas, and the screening of said hybridomas by ELISA (column 13, lines 6-42, column 15, lines 58-64) or immunoprecipitation or Western blot (column 17, lines 3-7). Cashman et al teach fusion of the spleenocyte with immortalized mouse cells (column 13, lines 17-19), and test kits for the diagnosis of prion disease comprising the epitope specific anti-prion antibodies (column 21, line 38 to column 22, line 5). Cashman et al teach the treatment of prion disease comprising the administration of the anti-prion monoclonal antibodies (column 26, lines 11-36) and pharmaceutical compositions (column 27, line 24 to column 28, line 21).

Lusslow et al teach that HSP70 can substitute for a carrier molecule and induce a strong B cell response without the need for adjuvants as required for other carrier molecules (pages 2299-2300, under section 3.4).

It would have been prima facie obvious to substitute HSP70 for the carrier protein used by Cashman et al. One of skill in the art would have been motivated to do so by the teachings of Lusslow et al on the ability of HSP70 to provide a carrier effect and the induction of a strong antibody response.

Claims 1-3, 8-10, 13, 75, 80-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cashman et al and Lussow et al as applied to claims 1-3, 8-10 and 13 above, and further in view of Raven et al (WO 03/080665).

It is noted that in the prior claim set, the prior protein was defined as consisting of SEQ ID NO:6 which would not read on a protein comprising SEQ ID NO:6. Claim 75 has now been amended to encompass a prion protein peptide selected from the group consisting of SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:9 which fails to limit the proteins in the group to prion

proteins consisting of SEQ ID NO:6, 7 or 9 versus prion peptides comprising SEQ ID NO:6, 7 or 9.

The combination of Cashman and Lussow et al renders obvious the claims to the extent that they are drawn to a method of producing a monoclonal antibody specific to a prion protein peptide comprising conjugating the prion protein peptide to Hsp70. The combination does not teach or suggest a prion protein peptide comprising SEQ ID NO:6.

Raven et al teach antibodies that bind to the peptide of SEQ ID NO:3 (claim 5) , wherein said SEQ ID NO:3 comprises the instant SEQ ID NO:6 peptide at residues 2-13.

It would have been prima facie obvious to use the SEQ ID NO:3 peptide in a fusion protein comprising Hsp70. One of skill in the art would have been motivated to do so by the teachings of Raven et al on the ability of the SEQ ID NO:3 peptide to elicit antibodies.

Claims 1-3, 8-10, 13, 75, 76, 80-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cashman et al, Lussow et al and Raven et al as applied to claims 1-3, 8-10, 13, 75, 77, 80-83 above, and further in view of Lawrence (U.S. 4,859,613).

Claim 76 embodies the method of claim 75 wherein glutaraldehyde is used for the chemical conjugation.

Cashman et al teach the limitations of claims 1, 3, 4, 8-10, 13-25, 75 and 81-83 as set forth above. Cashman et al do not specifically teach the conjugation of the prion proteins to carrier molecules using glutaraldehyde.

Lawrence teaches the use of glutaraldehdye for chemical conjugation of a hapten to the carrier protein of KLH, wherein glutaraldehdye was selected because only monomers of the hapten can be attached to the carrier due to the presence of only one reactive group for the crosslinking reagent, leaving the antigenicity of the hapten intact (column 4, line 59 to column 5, line 27).

It would have been prima facie obvious to use glutaraldehyde to conjugate the prion proteins to the Hsp70 using glutaraldehyde. One of skill in the art would have been motivated to do so by the teachings of Lawrence et al on the advantage of using glutaraldehyde for conjugations which avoids altering the antigenicity of the hapten.

Claims 1-3, 6, 8-10, 13, 85 and 87-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seiki et al (U.S.6,191,255) in view of Lussow et al (European Journal of Immunology, 1991, Vol. 21, pp. 2297-2302).

Seiki et al teach a method of making antibodies to MMP3 comprising immunizing an animal with MM3 conjugated to a carrier molecule (abstract, column 18, lines 27-36 and lines 40-41, column 18, line 63 to column 19, line 18). Seiki et al teach that mouse myeloma cells are used for cell fusions to produce hybridomas (column 19, line 62 to column 20, line 5). Seiki et al teach that B cells are isolated from lymph nodes, or spleen (column 20, lines 22-27). Seiki et al teach immortalized mouse cells including SP2/0-Ag14 for making the fused cells of the hybridomas (column 19, line 62 to column 20, line 5 and column 34, lines 6-7). Seiki et al teach that an ELISA was used to isolate the desired MM3 binding antibodies (column 35, lines 7-10)

Lusslow et al teach that HSP70 can substitute for a carrier molecule and induce a strong B cell response without the need for adjuvants as required for other carrier molecules (pages 2299-2300, under section 3.4).

It would have been prima facie obvious to substitute HSP70 for the carrier protein used by Seiki et al. One of skill in the art would have been motivated to do so by the teachings of Lusslow et al on the ability of HSP70 to provide a carrier effect and the induction of a strong antibody response.

Claims 1-3, 6, 8-10, 13, 85-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seiki et al and Lussow et al as applied to claims 1-3, 6, 8-10, 13, 85 and 87-89 above, and further in view of Lawrence (U.S. 4,859,613).

Seiki et al do not specifically teach the conjugation of the MM3 proteins to carrier molecules using glutaraldehyde.

Lawrence teaches the use of glutaraldehdye for chemical conjugation of a hapten to the carrier protein of KLH, wherein glutaraldehdye was selected because only monomers of the hapten can be attached to the carrier protein due to the presence of only one reactive group for

the crosslinking reagent, leaving the antigenicity of the hapten intact (column 4, line 59 to column 5, line 27).

It would have been prima facie obvious to use glutaraldehyde to conjugate the MM3 proteins to the Hsp70 using glutaraldehyde. One of skill in the art would have been motivated to do so by the teachings of Lawrence et al on the advantage of using glutaraldehyde for conjugations which avoids altering the antigenicity of the hapten.

Claim 84 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fillit et al (Journal of Experimental Medicine, 1986, Vol. 164, pp. 762-776) in view of Berzofsky et al, ('Antigen-Antibody Interactions and Monoclonal antibodies', In: Fundamental Immunology, W.E. Paul, Ed. 1993, page 458), Lussow et al (European Journal of Immunology, 1991, Vol. 21, pp. 2297-2302) and Yokoyama ('Production of Monoclonal Antibodies', In: Current Protocols in Immunology, 1991, Unit 2.5).

Claim 84 is drawn to a method comprising chemically conjugating hyaluronic acid to a carrier molecule; immunizing an animal with the conjugate; harvesting B cells from the animal; creating a hybridoma from the harvested B cells and screening the hybridomas for specificity to native hyaluronic acid.

Fillit et al teach a method for immunizing animals to obtain antiserum to hyaluronic acid comprising immunizing rabbits with formalinized encapsulated streptococci. Fillit et al teach that previous attempts to raise antibodies using hyaluronate conjugated to BSA were unsuccessful (page 762, lines 2-6). Fillit et al did not produce monoclonal antibodies.

Berzofsky et al teaches that monoclonal antibodies can be made reproducible in large quantities offering an advantage over polyclonal antiserum (page 458 under the heading of "Applications of Monoclonal Antibodies").

Yokoyama et al teaches the basic protocol for the production of monoclonal antibodies which includes fusion of spleen cells taken from the immunized animal to create a hybridoma and screening the hybridomas for specificity to the native antigen.

Lusslow et al teach that HSP70 can substitute for a carrier molecule and induce a strong B cell response without the need for adjuvants as required for other carrier molecules (pages 2299-2300, under section 3.4).

It would have been prima facie obvious to conjugate HSP70 to hyaluronate in place of the prior art BSA conjugated to hyaluronate to immunize an animal for the production of monoclonal antibodies One of skill in the art would have been motivated to do so by the teachings of Berzofsky et al on the advantages of having a monoclonal antibody which binds to the antigen of interest over polyclonal antiserum; the teachings of Yokoyama et al on the standard procedure used to produce a monoclonal antibody and the teaching of Lusslow et al on the ability of HSP70 to provide a carrier effect and the induction of a strong antibody response. One of skill in the art would understand that substitution of HSP70 for BSA would have a reasonable expectation of producing an antibody titer in an immunized animal.

Claims 1-3, 5, 8-10, 13, 26, 27, 32, 33, 35, 36, 39-42, 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zatsepina et al (Oncogene, 1997, Vol. 14, pp. 1137-1145) and Yokoyama ('Production of Monoclonal Antibodies', In: Current Protocols in Immunology, 1991, Unit 2.5) Lussow et al (European Journal of Immunology, 1991, Vol. 21, pp. 2297-2302) and Wu et al (U.S. 2004/0086845).

Zatsepina et al teach a method of making the monoclonal antibodies of TVGY701 and TVGY703 which specifically bind the E7 oncoprotein comprising immunizing mice with a purified recombinant E7 protein (page 1138 under "Generation of HPV 16 E7 Monoclonal Antibodies" and page 1144, under the heading of "Antibodies"). Zatsepina et al teach that hybridomas were screened by ELISA, immunoblot and immunoprecipitation. Zatsepina et al do not specifically teach the details of the hybridoma formation. Zatsepina et al do not teach immunization with a HSP70-E7 fusion protein..

Yokoyama teaches the details of forming a hybridoma comprising fusing spleen cells obtained from immunized mice with immortalized mouse myeloma cells.

Wu et al teach that E7 oncoprotein is a weak immunogen (paragraph [0007]).

Lusslow et al teach that HSP70 can substitute for a carrier molecule and induce a strong B cell response without the need for adjuvants as required for other carrier molecules (pages 2299-2300, under section 3.4).

It would have been prima facie obvious to immunize the mice with E7 fused to HSP70. One of skill in the art would be motivated to do so by the teachings of Wu et al on the low immunogenicity of the E7 protein and the teachings of Luslow et al on the strong induction of antibodies using HSP70 as a carrier for antigen. One of skill in the art would be motivated to make the hybridomas by the method of Yokoyama because the method is a standard protocol.

Claims 1-3, 5, 6, 8-10, 13, 26, 27, 32, 33, 35, 36, 37, 39-42, 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zatsepina et al, Lussow et al, Wu et al and Yokoyama as applied to claims 1-3, 5, 8-10, 13, 26, 27, 32, 33, 35, 36, 39-42, 45 above, and further in view of Seiki et al (U.S.6,191,255).

Claims 6 and 37 embody the methods of claims 1 and 26, respectively, wherein the B cells are harvested from lymph nodes.

The combination of Zatsepina et al, Lussow et al, Wu et al and Yokoyama renders obvious the instant methods wherein the B cells are harvested from the spleen. The combination does not teach harvesting B cells from the lymph nodes.

Seiki et al teach that B cells can be harvested from the spleen or the lymph nodes (column 20, lines 22-27).

It would have been prima facie obvious at the time that the invention was made to harvest antigen-primed B cells from the lymph nodes. One of skill in the art would have been motivated to do so by the teachings of Seiki et al which indicate that lymph nodes provide antigen-primed B cells for hybridoma fusions as well as spleen cells

Claims 1-3, 5, 8-10, 13, 26, 27, 32, 33, 35, 36, 39-42, 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zatsepina et al, Lussow et al, Wu et al and Yokoyama as applied to claims 1-3, 5, 8-10, 13, 26, 27, 32, 33, 35, 36, 39-42, 45 above, and further in view of Burnett et al ('Human Monoclonal antibodies to Defined Antigens', In: Human Hybridomas and Monoclonal Antibodies, Engleman et al, Ed.s, 1985, page 115)

Claims 7 and 38 embody the methods of claims 1 and 26, respectively, wherein B cells are harvested from the blood.

Burnett et al teach peripheral blood as a source of B cells after vaccination (pages 115).

It would have been prima facie obvious at the time that the claimed invention was made to use peripheral blood as a source of B cells for the production of hybridomas. One of skill in the art would have been motivated to do so by the teachings of Burnett et al noting this source of antigen-primed lymphocytes and because accessing blood is more convenient that removing the spleen or lymph nodes of an animal.

Claims 1-3, 5, 8-10, 13, 26, 27, 31-33, 35, 36, 39-42, 45are rejected under 35 U.S.C. 103(a) as being unpatentable over Zatsepina et al, Lussow et al, Wu et al and Yokoyama as applied to claims 1-3, 5, 8-10, 13, 26, 27, 32, 33, 35, 36, 39-42, 45 above, and further in view of Zwerschke et al (WO 2003/080669).

Claim 31 embodies the method of claims 27 wherein the host cell is E coli.

Zatsepina et al teaches the use of recombinant E7 isolated from yeast. Zatsepina et al does not teach the use of recombinant E7 protein isolated from E coli.

Zwerschke et al (WO 2003/080669) teach highly purified E7 protein isolated from E coli, page 9, lines 13-15 and 27-30 and page 12, lines 3-12).

It would have been prima facie obvious at the time that the claimed invention was made to isolate the highly purified E7 protein from E coli.. One of skill in the art would have been motivated to do so because E coli is a common cloning vector and because the expression of the protein in E coli was verified by Zwerschke et al.

Claims 1-3, 5, 8-10, 12, 13, 26, 27, 32, 33, 35, 36, 39-42, 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zatsepina et al, Lussow et al, Wu et al and Yokoyama as applied to claims 1-3, 5, 8-10, 13, 26, 27, 32, 33, 35, 36, 39-42, 45 above, and further in view of Milstein ('Monoclonal Antibodies from Hybrid Myelomas', In: Monoclonal Antibodies in Clinical Medicine, McMichael and Favre, Ed.s, 1982, page 9).

Claims 12 and 44 embody the methods of claims 1 and 26, respectively, wherein the hybridoma is created using an immortalized rat cell.

Milstein teaches that hybridomas can be made by fusing rat or mouse spleen cells with rat myeloma cells (page 9, Table 1.1).

It would have been prima facie obvious at the time that the claimed invention was made to use rat myeloma cells as the immortalized cell in the method rendered obvious by the combination of Zatsepina et al, Lussow et al, Wu et al and Yokoyama. One of skill in the art would have been motivated to do so by the teachings of Milstein on the successful combination of rat myeloma cells with either mouse or rat spleen cells for the production of hybridomas secreted immunoglobulin.

Applicant argues against all obviousness type rejections in combination with Lussow stating that Lusslow requires that the mice be previously primed with live BCG. this has been considered but not found persuasive because the instant claims do not exclude the priming of the mammal with BCG before immunization.

All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicant's amendments.

Claims 77-79 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643